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**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1654729> since 2017-12-14T11:26:12Z

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The Challenges of Optimising Immuno and Targeted Therapies  
**From Cancer Biology to the Clinic**  
EACR European Association for Cancer Research AACR American Association for Cancer Research SOCIETÀ ITALIANA DI CANCEROLOGIA



## **Unraveling the potential role of autophagy in CD157-associated chemoresistance in malignant pleural mesothelioma.**

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**Introduction.** Resistance of cancer cells to cytotoxic agents is a major challenge in malignant pleural mesothelioma (MPM) patient management. Recently, we demonstrated that the CD157 glycoprotein is expressed by ~80% of MPM surgical specimens and its expression levels correlate with poor prognosis. *In vitro*, high CD157 expression has been associated with enhanced cell growth, migration, invasion and activation of the PI3K/Akt/mTOR pathway leading to resistance to platinum-based chemotherapy. The inhibition of mTOR with Everolimus or of both PI3K and mTOR with BEZ-235 proved to be able to revert chemoresistance in CD157-positive cells. As increasing evidence indicates that autophagy has a key role in platinum-based chemotherapy resistance, in this study we investigated the potential implication of autophagy in CD157-mediated chemotherapy resistance in MPM.

**Materials and methods.** CG98 (CD157-positive) and MSTO-211H (CD157-negative) MPM cell lines (both native and engineered for CD157 expression), were used as models, to study apoptosis and autophagy. Using Western blot and immunofluorescence, we analysed the expression of caspase-3 and PARP, as hallmarks of apoptosis, and of LC3II, a protein associated with autophagosomes. Cell proliferation in the presence or absence of Chloroquine (CQ) and Bafilomycin autophagy inhibitors was assessed by PrestoBlue Cell Viability assay.

**Results and discussion.** Treatment with cisplatin (CDDP) induced a more robust caspase-3 activation and PARP cleavage in CD157-negative than in CD157-positive cells, suggesting that CD157-associated resistance is at least partly related to an impaired apoptotic response. Moreover, treatment with CQ or Bafilomycin induced greater accumulation of LC3II and had a stronger growth inhibitory effect in CD157-positive than in CD157-negative cells, indicating that autophagy could act as a prosurvival mechanism contributing to CD157-associated drug resistance. Preliminary results showed that CDDP treatment, alone or in combination with autophagy inhibitors, promotes high levels of autophagy in CD157-positive cells, corroborating the notion that CDDP is able to elicit the autophagic flux in platinum-resistant cells.

**Conclusion.** These results support the rationale to hypothesize the implication of autophagy in CD157-associated resistance and highlight the potential clinical utility of CD157 as a marker for selecting patients with particularly aggressive MPM who might benefit from a combined therapy.